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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/719,540
Filing Date: November 20, 2003
Appellant(s): HALE ET AL.

Ms. Margaret M. Wall, Esq.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 1, 2010 appealing from the Office action mailed February 1, 2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 1, 5-9, and 12-24 are pending. Claims 21-23 are withdrawn from consideration, as being drawn to a non-elected invention. Claims 1, 5-9, 12-20, and 24 stand rejected.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The provisional obviousness-type double patenting rejection of claims 1 and 5-15 over claims 1 and 15 of Application No. 11/346,548 (copending '548) is withdrawn because copending '548 is abandoned.

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

5,284,133	Burns et al.	2-1994
7,040,314	Nguyen et al.	5-2006
US 2004/0009128	Rabinowitz et al.	1-2004

6,716,416	Rabinowitz et al.	4-2004
7,585,493	Hale et al.	9-2009
7,645,442	Hale et al.	1-2010
6,716,416	Rabinowitz et al.	4-2004

Drug Information Handbook, 2nd edition, Lexi-Comp, Inc.: Cleveland, 1994-1995, pp 554-555.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

I. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham **v.** John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Appellant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

(A) Claims 1, 5-9, 12-15, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burns et al. (U.S. Patent No. 5,284,133) in view of Drug Information Handbook, 2nd edition (Lexi-Comp, Inc.: Cleveland, 1994-1995, pp 554-555) ("DIH") for the reasons of record set forth on pages 11-12 of the office action mailed on June 2, 2006 and restated below.

Appellant Claims

Appellant claims a method of treating headache comprising administering to a subject in need of treatment an effective amount of loxapine, loxapine prodrugs, or pharmaceutically acceptable salts thereof, wherein the dosage of loxapine is from about 0.3 to about 20 mg, and administration has the property of resulting in maximal loxapine serum concentration within 15 (claim 13) or 30 (claim 12) minutes of delivery so as to result in a peak rate of increase in blood levels of at least about 1 ng/ml/minute (claim 14) and/or a loxapine blood level of at least about 5 ng/ml within about 15 minutes of administration (claim 15).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Burns teaches an inhalation device provided with a mechanism to assure patient compliance with a drug dosage regimen (abstract) and that patient non-compliance with inhalation devices has been recognized as a major medical problem (col. 2, lines 39-40). Burns

teaches an inhalation device as well as an actuator/timing controller that operates in conjunction with an inhalation device to prevent both patient under compliance with prescribed dosing and patient abuse or dependence on prescribed medication (col. 1, lines 19-24). Burns also teaches that many drugs, which are traditionally delivered by intravenous, subcutaneous, intramuscular, or intraperitoneal injection, can advantageously be delivered by aerosol inhalation. Delivery of a drug to the alveoli in the lung to a point where the drug can pass through the lung mucosa can be accomplished with an MDI, nebulizer, dry powder inhaler, or like device which operates by a patient inspiring solubilized or micronized drug deep into the lung. In order for the drug to penetrate deeply in the lung, the particles containing the drug should be on the order of a few microns (0.2 to 20) in size. Aerosol delivery is particularly advantageous because first-pass metabolism of the drug by the liver and kidneys is avoided. In addition, the objectionable requirement of finding a suitable injection site and piercing the skin with a needle is avoided. Furthermore, a wide variety of systemically active drugs would benefit from aerosol delivery via inhalation, including neuroleptics, psychotropic drugs, and narcotic antagonists, analgesics, etc (col. 5, lines 29-57). In addition, as delivering systemic drugs by aerosol administration gains wider acceptance, there will be increased demands on the safety of inhalation devices. It is expected that with some drugs, relying on proper patient aerosol administration will not be acceptable. For example, with headache analgesics, including, loxapine hydrochloride, there may be a tendency of some patients to overdose themselves (col. 7, lines 3-5, 10-17, and 27-30). Burns states that his invention is specifically directed to providing inhalation devices, such as MDIs, nebulizers, and dry powder inhalers, with a safety alarm and actuator mechanism which

both aids in assuring that a patient administers in a timely manner a required dose of drug and prevents overdosing a prescribed drug (col. 7, lines 40-45).

The DIH teaches different oral dosages of loxapine for adults of 10 mg twice daily or more as needed to control psychotic symptoms; that the usual dose range is 60-100 mg/day divided in doses taken 2-4 times/day (i.e. single dosages ranging from 15-25 mg); and that dosages greater than 250 mg/day are not recommended. For I.M. administration the recommended dosages are 12.5-50 mg every 4-6 hours or longer as needed and change to oral therapy as soon as possible (pg 555 of DIH).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Burns lacks the teaching of loxapine dosages. This deficiency is cured by the teachings of the DIH.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been apparent to a person of ordinary skill in the art at the time of the instant invention that one could utilize Burn's inhalation device to deliver loxapine hydrochloride in the practice of a method of treating headache, because loxapine hydrochloride is a known headache analgesic. A skilled artisan would have been motivated to deliver loxapine hydrochloride to treat headache pain (including migraine pain), because this use of loxapine hydrochloride (LoxHCl) is taught by Burns. A skilled artisan would have been further motivated

to select LoxHCl because it is expected that there may be a tendency of some patients to overdose themselves with CNS-affecting drugs, including LoxHCl; and because Burn's device is designed to administer drugs via the inhalation administration of aerosols while assuring proper dosing and preventing overdosing. Regarding the distinction between different types of headache pain, it would have been obvious to a skilled artisan that LoxHCl would be useful in the treatment of these different kinds of headaches/migraines, because it is a known headache analgesic. It is art recognized that analgesics relieve pain.

It would have been obvious to a person of ordinary skill in the art at the time of the instant application to combine the teachings of Burns and the DIH, because the DIH is a well-known reference for commercially available therapeutic agents. Regarding the dosages taught by the DIH, it would have been apparent to a skilled artisan that the dosages required for inhalation administration would be lower than those for oral administration, because via inhalation administration the disadvantage of first-pass metabolism of the drug by the liver and kidneys is avoided (Burns). Therefore, a lower amount of drug would be needed if administered by inhalation. The skilled artisan would utilize the teachings of the DIH regarding the oral doses as a maximum starting point from which to undertake routine optimization of dosage amounts as practiced in the art. A person of ordinary skill in the art would have had a reasonable expectation of success upon combination of the prior art references, because Burns teaches the inhalation administration of LoxHCl as a headache analgesic and the DIH provides the skilled artisan with guidance as to adverse reactions, overdose/toxicology, dosage recommendations, drug interactions, pharmacodynamics of loxapine needed to effectively and safely administer said drug. Regarding the properties associated with inhalation administration, such as systemic

delivery of drug and rapid attainment of maximal loxapine serum concentrations in specific periods of time, it would have been apparent to a skilled artisan at the time of the instant invention that these properties are characteristic of inhalation administration, as the Appellant admits on page 13, paragraph [0041], of the instant specification.

(B) Claims 16-17 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burns et al. (U.S. Patent No. 5,284,133) in view of Drug Information Handbook, 2nd edition (Lexi-Comp, Inc.: Cleveland, 1994-1995, pp 554-555) ("DIH"), as applied above to claims 1, 5-9, 12-15, and 24 and further in view of Nguyen et al. (U.S. Patent No. 7,040,314) for the reasons of record set forth on pages 12-15 of the office action mailed on June 2, 2006 and restated below.

Appellant Claims

Appellant claims a method of treating headache comprising administering to a subject in need of treatment an effective amount of loxapine, loxapine prodrugs, or pharmaceutically acceptable salts thereof, wherein loxapine or pharmaceutically acceptable salt/prodrug thereof is administered via inhalation using a rapid-heating delivery article or a thin-film drug delivery article (claim 16), wherein said compound is vaporized and condensed to provide at least 50% recovery of said compound in an aerosol containing less than about 5% w/w degradation products.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Burns have been set forth above. Nguyen teaches an aerosol generating device that generates an aerosol by passing liquid aerosol formulation through a flow passage heated to convert the liquid into a vapor, which is mixed with air to form an aerosol, wherein

said device can be incorporated in a hand held inhaler. In some embodiments, particles of the aerosol consist essentially of the second component. The aerosol can be delivered to a targeted portion of the lung using the inhaler (abstract). The liquid aerosol formulations include at least one high volatility carrier, preferably a liquid solvent, and a second component, which is a solute dissolved in the liquid carrier, including any suitable medicament that may be delivered to a patient by an aerosol. Suitable medicaments include analgesics and anxiolytics (e.g. loxapine) (col. 3, lines 49-52; col. 4, lines 58-67; col. 5, line 26, and claims 18-20). Nguyen teaches that the aerosol-generating device preferably generates aerosols in which 95% of the aerosol particles (aerosol droplets) have a size between 0.5 microns to about 2.5 microns, and that the aerosol may contain particles with sizes less than 0.1 microns (col. 15, lines 20-25). In Example 1 and Figure 7, Nguyen teaches that the aerosols generated from a 1% albuterol ethanolic solution by the invented device had an average MMAD of 0.66 microns. Nguyen's claims 18, 20, 26, and 28 recite a method of generating an aerosol, wherein the second component is a medicament, the aerosol is a condensation aerosol and that the aerosol particles having a MMAD of less than 2.5 microns, respectively. In Example 7, Nguyen stated that the test results depicted in Fig. 11 demonstrated that the aerosol generating device can be used to prepare budesonide aerosols with up to 100% recoveries, no observable degradation, and sufficiently small particle sizes for inhalation, using a carrier, including ethanol.

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

Burns lacks the teaching of a rapid-heating drug delivery article. This deficiency is cured by the teachings of Nguyen.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Burns and Nguyen, because Burns teaches an inhalation device as well as an actuator/timing controller that operates in conjunction with an inhalation device to prevent both patient under compliance with prescribed dosing and patient abuse or dependence on prescribed medication. The inhalation devices specifically suited for use in combination with Burns teachings include metered-dose inhalers, nebulizers, and dry powder inhalers. Both MDIs and nebulizers are art recognized to deliver aerosols generated from liquid formulations and Nguyen teaches an aerosol generating device wherein formulations comprising a liquid carrier and a medicament are heated to generate aerosols suitable for inhalation administration and characterized by high recovery percentages and very low amounts of degradation products. Therefore, it would have been apparent to a skilled artisan at the time of the instant invention that one could combine the teachings of Burns, suitably used with both MDIs and nebulizers, and have a reasonable expectation of successfully delivering drugs, including loxapine, as aerosols having desirable aerodynamic properties (low MMAD, high recovery, low amount of degradation products) and in such a manner as to improve patient dosage compliance and prevent patient overdose.

(C) Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burns et al. (U.S. Patent No. 5,284,133) in view of Drug Information Handbook, 2nd edition (Lexi-Comp, Inc.: Cleveland, 1994-1995, pp 554-555) ("DIH") as applied to claims 1, 5-9, 12-15, and 24, and further in view of Rabinowitz et al. (US 2004/0009128) for the reasons of record set forth on pages 15-17 of the office action mailed on June 2, 2006 and restated below.

Appellant Claims

Appellant claims a method of treating headache comprising administering to a subject in need of treatment an effective amount of a loxapine compound, loxapine prodrugs, or pharmaceutically acceptable salts thereof, wherein loxapine or pharmaceutically acceptable salt/prodrug thereof is administered via inhalation using a thin-film drug delivery article (claim 16), wherein said compound is vaporized and condensed to provide at least 50% recovery of said compound in an aerosol containing less than about 5% w/w degradation products (17), and said loxapine compound is coated on a substrate as a thin film having a film thickness between 0.5 and 20 microns (claim 18).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Burns have been set forth above. Rabinowitz discloses a method of delivering an amine drug in an aerosol form is comprising: a) heating a coating (i.e. a film), which includes an amine drug salt on a substrate contained in a device to a temperature sufficient to volatilize the amine drug from the coating, b) by said heating, forming an amine drug vapor, and c) during said heating, drawing air through said device, condensing said vapor to form aerosol particles containing less than 10% degradation products of the compound (abstract).

Rabinowitz also teaches that in more preferred embodiments, the coating of the amine drug salt used has a thickness between about 0.5 and 20 microns, and the aerosol particles generated have a mass median aerodynamic diameter between about 1 and 5 micrometers [0025]. Loxapine is an amine drug, and is identified by Rabinowitz in [0063] as an example of a suitable drug for use in his invention from which an amine salt may be formed. The drug amine salts selected for vaporization preferably have the following characteristics: a molecular weight greater than 200 g/mole and a decomposition index less than 0.15. Typical examples of such preferred drug amine salts that are anxiolytics include loxapine [0100]. In Examples 3-4, Rabinowitz teaches general methods of screening drug amines (Example 3) and drug amine salts (Example 4) for aerosolization preferability. In Example 5, Rabinowitz teaches that aerosols formed by his method have an MMAD ranging from 1-3 microns.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Burns lacks the teaching of a thin-film drug delivery article. This deficiency is cured by the teachings of Rabinowitz.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Burns and Rabinowitz, because Burns teaches an inhalation device as well as an actuator/timing controller that operates in conjunction with an inhalation device to prevent both patient under compliance with prescribed dosing and patient

abuse or dependence on prescribed medication. A skilled artisan would have been motivated to combine the teachings of Burns and Rabinowitz, because it is expected that with some drugs, relying on proper patient aerosol administration will not be acceptable, such as, headache analgesics, including, loxapine hydrochloride, which may also suffer from a tendency in some patients to overdose themselves (Burns, col. 7, lines 3-5, 10-17, and 27-30). It would have been apparent to a skilled artisan at the time of the instant invention that one could combine the teachings of Burns, suitable for use with inhalation devices, and have a reasonable expectation of successfully delivering drugs, including loxapine, as aerosols having desirable aerodynamic properties (low MMAD and a low amount of degradation products) and in such a manner as to improve patient dosage compliance and prevent patient overdose. Rabinowitz' device is an inhalation device, therefore, a person of ordinary skill in the art would have had a reasonable expectation of success upon combination of the prior art references.

II. Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

(IIA) Claims 1, 16-17, and 19 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7, 9, 10, 12, and 13 of U.S. Patent No. 6,716,416 (USPN '416) for the reasons of record set forth on pages 17-18 of the office action mailed on June 2, 2006, restated below, and because no terminal disclaimer has yet been filed by Applicants.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are overlapping in scope and mutually obvious. The claims of USPN '416 encompass the steps of generating the condensation aerosol obviously encompassed by the steps incorporated in the administration of loxapine as described in claims 16-20 of the instant application, wherein loxapine is volatilized using a thin film drug delivery article by heating a film to generate condensation particles comprising less than 5% degradation particles (e.g. at least about 97% loxapine).

(IIB and IIC) Claims 1 and 16-20 (claim 20, only with copending '877) are rejected as being unpatentable over (1) claims 12, 15, 16, and 18 of copending Application No. 10/633,876 (copending '876)[1] and (2) claims 1 and 7 of copending Application No. 10/633,877 (formerly

[1] Copending Application No. 10/633,876 issued as U.S. Patent No. 7,645,442 on January 12, 2010 and claims 12, 15-16, and 18 of copending '876 correspond to claims 12, 15-16, and 18 of issued U.S. Patent No. 7,645,442.

copending '877, now allowed application '877)[2] for the reasons of record set forth on pages 18-19 of the office action mailed on June 2, 2006, restated below, and because no terminal disclaimer has yet been filed by Applicants.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are overlapping in scope and mutually obvious. The claims of copending '876 encompass the steps of generating the condensation aerosol obviously encompassed by the steps incorporated in the administration of loxapine as described in claims 16-20 of the instant application, wherein loxapine is volatilized by heating a thin film having a thickness ranging from between 0.05 to 20 microns and comprising a loxapine film on a substrate contained within a drug delivery article that generates condensation aerosol particles comprising less than 5% degradation particles Similarly, the cited claims of copending '877 are drawn to an article for use in an aerosol device comprising a drug composition film (i.e. loxapine) having a film thickness between 0.05-20 microns, which upon heating generates a condensation aerosol comprising less than 5% degradation products. Therefore, the examiner concludes that claims 12, 15, 16, and 18 of copending Application No. 10/653,876 (copending '876) and claims 1 and 7-9 of copending Application No. 10/633,877 (copending '877) prima facie obvious over claims 1 and 16-20 (claim 20, only with copending '877) of the instant application.

(10) Response to Argument

[2] Copending Application No. 10/633,877 (copending '877) issued as U.S. Patent No. 7,585,493 on September 9, 2009. Claims 1 and 7 of copending '877 correspond to claims 1 and 7 in issued U.S. Patent No. 7,585,493. Claims

(A) Response to Appellants' traversal of the rejection of claims 1, 5-9, 12-15, and 24 under 35 U.S.C. 103(a) as being unpatentable over Burns et al. (U.S. Patent No. 5,284,133) in view of Drug Information Handbook, 2nd edition (Lexi-Comp, Inc.: Cleveland, 1994-1995, pp 554-555) ("DIH").

Appellants traverse the rejection of claims 1, 5-9, 12-15, and 24 under 35 U.S.C. 103(a) as being unpatentable over Burns et al. (U.S. Patent No. 5,284,133) in view of Drug Information Handbook, 2nd edition (Lexi-Comp, Inc.: Cleveland, 1994-1995, pp 554-555) ("DIH") by arguing that (1) allegedly none of the cited references teach the administration of loxapine to treat headache; (2) allegedly none of the cited references teach or suggest a loxapine dosage of 0.3-6.0 mg; and (3) it is unexpected that loxapine could be effective in treating pain.

The Examiner respectfully disagrees with Appellants' traversal arguments. Regarding (1), the passage from Burns (i.e. col. 7, lines 12-19), which Appellants dispute teaches that loxapine hydrochloride is recognized as a headache analgesic is displayed below:

> be acceptable. For example, with neuroleptics, psychotropics, narcotic antagonists, other central nervous system (CNS) drugs and headache analgesics, such as prochlorperazine, fluphenazine hydrochloride, chlorpromazine, trifluperazine hydrochloride, thioridazine hydrochloride, loxapine hydrochloride, and haloperidol decanoate, anxiolytics such as alprazolam, buspirone and diazepam; antidepressants such as amitriptyline,

The plain meaning of the words utilized by Burns is that loxapine hydrochloride is a headache analgesic. The phrase, "such as," conventionally introduces exemplary species of a given group. In this case, the comma after the words "headache analgesics" followed by the phrase "such as" clearly introduces a short list of drugs recognized as headache analgesics by

8-9 of copending '877 were cancelled during prosecution of this copending application.

Burns. To support their argument, Appellants cite non-patent literature publications by (i) Kelly and (ii) Bowden, which do not contain any mention of the use of loxapine as a headache analgesic. These references are not found persuasive, because it is not unexpected that a known active agent may have multiple pharmaceutical uses, as Appellants concede in their arguments at the first full paragraph on page 5 ("…[T]he list of pharmaceuticals in the disputed passage [of Burns] were known to be antipsychotics and may have had other applications."). The fact that Burns clearly states that loxapine is a headache analgesic is not contravened by the fact that Kelly and Bowden teach that some of the other drugs mentioned in Burns' list of headache analgesics were also suitable to treat other conditions, such as asthma (e.g. trifluoperazine). Appellants' argument is unpersuasive.

Regarding (2), the combined prior art teachings establish that the inhalation administration of an active agent is advantageous over other administration routes, because it avoids the first pass metabolism of the drug (Burns) and consequently a lower dosage of a drug may be used. The teachings of the DIH establish dosages of loxapine that were previously approved for the treatment of psychotic disorders and said dosages would provide the ordinary skilled artisan with a starting point from which to optimize the dosage of loxapine in the treatment of headaches per Burns' clear teachings that loxapine is a headache analgesic. Appellants' argument seems to be based on the lack of an explicit teaching of the same dosage of loxapine in the combined prior art. However, the prior art provides the ordinary skilled artisan with ample motivation and guidance to reduce the dosage of loxapine from that which was known to be suitable when delivered by non-inhalation administration routes in the treatment of psychotic disorders. An ordinary skilled artisan in the process of optimizing loxapine inhalation

dosage amounts would be motivated to test lower dosages of loxapine, because it was well known at the time of the instant invention that less drug is necessary to obtain clinical efficacy when a drug is administered by inhalation administration due to the recognized latent advantages of inhalation administration. Moreover, the determination of an optimal dosage once a drug has been identified as suitable for a particular treatment, such as providing headache analgesia (Burns), is well within the skill of the ordinary artisan. Therefore, because the prior art teachings that loxapine is a headache analgesic, suggests its inhalation administration, and recognizes that inhaled drugs require lower dosages to be clinically effective, the ordinary skilled artisan would have had a reasonable expectation of successfully ascertaining the dosages of loxapine that were clinically effective in the treatment of headache, such as migraine, when administered by inhalation, by optimizing the dosage of loxapine starting from the dosages already known in the art as being safe and effective for the treatment of other disorders. Appellants' allegation of unexpected results in the observation of loxapine being suitable as an analgesic is unpersuasive, because Burns explicitly identified loxapine as being a headache analgesic. It is well-known in the art that analgesics are suitable for the treatment of pain. Appellants do not provide evidence suggesting that analgesics were not routinely used for the treatment of pain or that the ordinary skilled artisan cognizant of Burns' clear teachings that loxapine is a headache analgesic would reasonably expect its analgesic effects not to be clinically observable at the dosages recited in Appellants' claims. Thus, there is no basis to conclude that the observation that loxapine has analgesic properties is unexpected or surprising. In conclusion, Appellants' traversal arguments are unpersuasive and the aforementioned rejection is maintained.

(B) Response to Appellants' traversal of the rejection of claims 16-17 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burns et al. (U.S. Patent No. 5,284,133) in view of Drug Information Handbook, 2nd edition (Lexi-Comp, Inc.: Cleveland, 1994-1995, pp 554-555) ("DIH"), as applied above to claims 1, 5-9, 12-15, and 24 and further in view of Nguyen et al. (U.S. Patent No. 7,040,314).

Appellants traverse the instant rejection by alleging that Nguyen fails to cure the alleged deficiency that Burns fails to teach that loxapine is a headache analgesic; the combined prior art fails to teach or suggest a loxapine dosage of 0.3-6.0 mg; and Appellants have demonstrated that loxapine unexpectedly possesses analgesic properties (i.e. it controls pain). These traversal arguments were found unpersuasive, as explained above in section (A) (see pages 17-19 above). The Office's rebuttal of these traversal arguments is herein incorporated by reference. The rejection is maintained.

(C) Response to Appellants' traversal of the rejection of claims 16-18 under 35 U.S.C. 103(a) as being unpatentable over Burns et al. (U.S. Patent No. 5,284,133) in view of Drug Information Handbook, 2nd edition (Lexi-Comp, Inc.: Cleveland, 1994-1995, pp 554-555) ("DIH") as applied to claims 1, 5-9, 12-15, and 24, and further in view of Rabinowitz et al. (US 2004/0009128).

Appellants traverse the instant rejection by alleging that Rabinowitz fails to cure the alleged deficiency that Burns fails to teach that loxapine is a headache analgesic; the combined prior art fails to teach or suggest a loxapine dosage of 0.3-6.0 mg; and Appellants have demonstrated that loxapine unexpectedly possesses analgesic properties (i.e. it controls pain).

These traversal arguments were found unpersuasive, as explained above in section (A) (see pages 17-19 above). The Office's rebuttal of these traversal arguments is herein incorporated by reference. The rejection is maintained.

(IIA-IIC) Appellants have not traversed the rejections on the ground of nonstatutory obviousness-type double patenting over (i) of U.S. Patent No. 6,716,416 (USPN '416) (see pages 14-15 above), (ii) copending Application No. 10/633,876 (copending '876) [now U.S. Patent No. 7,645,442], and (iii) copending Application No. 10/633,877 (copending '877) [now U.S. Patent No. 7,585,493] and have indicated their intention to file terminal disclaimers (Appeal Brief at 3). Appellants' comments are understood as being a request to hold the obviousness-type double patenting rejections in abeyance. However, there is no provision in the MPEP wherein Appellants are permitted to request the holding of rejections in abeyance. Appellants must either traverse these rejections or concede to their propriety. The aforementioned obviousness-type double patenting rejections are maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

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